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ARTICLE

Aerosolized amikacin in patients with difficult-to-treat pulmonary nontuberculous mycobacteriosis

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Abstract Patients with pulmonary nontuberculous mycobacteriosis (pNTM) may have suboptimum response to conventional antimicrobial therapy. Aerosolized amikacin (aeAmk) was given to nine patients who had failed standard combination oral antimycobacterial drugs. A favorable toxicity profile, even in patients given aeAmk for an extended duration, median 75±85 (range, 18–277) days and total cumulative dose 35,400±30,568 (range, 7,600–95,400) mg, was encouraging, as was the clinical response and resolution of symptoms in 8 of 9 patients. The patient who failed therapy died due to complications arising from prior hematopoietic transplantation. The feasibility and efficacy of aeAmk in combination with oral anti-NTM drug(s) for treatment-refractory disease and, importantly, in primary therapy for pNTM requires validation randomized trials.

Introduction

Treatment response in patients with pulmonary nontuberculous mycobacteriosis (pNTM) is often unpredictable, despite the fact that immunotherapy with *Mycobacterium* vaccine was recently shown to only modestly influence outcomes following combination treatment with antimicrobial drugs [1]. Drug toxicity, drug–drug interaction, intolerance to prolonged therapy with multiple antimicrobial agents, and drug resistance pose as impediments for the successful management of these infections [2]. This is further complicated due to potential disconnect between in vitro drug susceptibility results and clinical response to NTM diseases for various species of nontuberculous mycobacteria [3]. Aerosolized drug administration has been an attractive drug delivery platform for pulmonary diseases and infections involving the distal bronchial tree and lungs. Bypassing conventional oral or parenteral drug administration reduces the potential for drug toxicity and concerns for drug–drug interaction [4]. Aerosolized amikacin (aeAmk) has been safely and successfully used in the treatment of severe Gram-negative pneumonia for critically ill immunocompetent and immunosuppressed cancer patients [4]. Here, safety and feasibility of aeAmk in patients with difficult-to-treat pNTM disease in an ambulatory infectious diseases clinic at a comprehensive cancer center is presented.

Materials and methods

The study was performed following approval from the MD Anderson Cancer Center Institutional Review Board. Patients had received aeAmk between 2004 and 2009.

Infections were considered difficult-to-treat or treatment-refractory if patients had: (a) failed to show clinical improvement in symptoms attributed to pNTM or(b) radiographic worsening on followup computed tomography (CT) scan of the thorax following 3 months or more of treatment with combination oral antimicrobial drugs to which mycobacteria were susceptible. Similarly, (c) patients who were unable to tolerate oral agents due to toxicity, adverse events, or interactions with other medications were regarded

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as the difficult-to-treat group and were given the option of a trial of inhaled amikacin in combination with one or two oral agents to which NTM had shown in vitro susceptibility.

The standard methods used for culturing mycobacteria, nucleic acid hybridization using a DNA probe (Gen-Probe, San Diego, CA) and sequencing analysis of a 645-base-pair fragment of the 16S rRNA gene (16S rDNA), were described previously [5].

Antibiotic susceptibility was assessed according to the guidelines of the Clinical and Laboratory Standard Institute (CLSI) [6, 7].

Standard definitions for pNTM disease as outlined by the American Thoracic Society (ATS) were used [8]. All values are given as median ± standard deviation (s.d.).

Inhaled amikacin

The methods of aerosol delivery of amikacin and treatment protocols are described in detail elsewhere [4]. Briefly, inhaled amikacin was prescribed as follows: the institutional pharmacy dispensed nebulized formulas made from commercially available intravenous preparation in the following strengths: amikacin (100 mg per 3-mL intravenous dose). Patients self-administered amikacin, 100 mg twice-daily was increased to 300 mg twice-daily if the initial low dose was tolerated without an adverse event. All first doses were given under careful observation of the respiratory therapist and a registered nurse, who carefully monitored the patient for immediate and early toxicity. Patients received inhaled beta-agonist bronchodilators before and after therapy.

Results

The patient and disease characteristics are shown in Table 1. The age of the patients was 63±9 years, 56% had a solid-organ cancer, and, in a patient (11%) with acute myelogenous leukemia, polymycobacterial lung infection occurred after undergoing matched related donor hematopoietic cell transplantation. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was 6±3. Three patients (33%) were receiving high-dose systemic corticosteroids. Bronchoalveolar lavage specimen provided diagnosis in 8 (89%) of the nine patients. CT scan findings showed that 67% of patients had both lungs involved, and lingula was also noted have been involved in 44% of patients with pNTM in this group. aeAmk was added to the first line antimicrobial therapy in 4 patients (44%) who had failed to show improvement on oral combination therapy alone. The in vitro amikacin susceptibility was known in six *Mycobacterium* isolates as follows: ≤16 mcg/ml (n=3), ≤8 mcg/ml (n=2), and ≤1 (n=1). The duration of aeAmk therapy was 75±85 (range, 18–277) days and the total cumulative dose given was 35,400±305,68 (range, 7,600–95,400) mg.

Features consistent with Lady Windermere syndrome, including postmenopausal women (>60 years) with chronic non-productive cough, gradually progressive bronchiectasis, thoracic structural abnormalities such as pectus excavatum, scoliosis of dorsal spines, and certain personality traits, including voluntary cough suppression and dysthymia, were present in six patients [9, 10]. Self-limiting hoarseness of voice, throat irritation, and bitter taste occurred in one patient each. In the patient with persistent throat irritation and cough after aerosolized drug treatments, symptoms improved after the dose was reduced from 300 mg to 100 mg twice-daily. All patients except one who died due to complications arising from allogeneic stem cell transplantation had a favorable clinical response.

Discussion

aeAmk was well-tolerated and, in nine patients, clinical improvement was encouraging, as standard anti-mycobacterial drug therapy had failed. The systemic therapy for pNTM disease has been fraught with serious limitations due to (a) drug toxicity associated with the prolonged administration of multiple drugs, (b) high cost of new-generation macrolides and respiratory fluoroquinolones, and (c) slow or lack of appreciable clinical improvement [2]. In six patients with slow-growing mycobacterial lung disease who had failed combination oral drug therapy, the addition of 15 mg/kg daily aeAmk plus standard macrolide-based combination therapy had been safe; clinical improvement, radiographic stabilization, and microbiologic cure in 5 of 6 patients was in concert with the observation presented in this report [11]. Infection recurrence is not uncommon in patients with slow-growing mycobacterial lung disease and Lady Windermere syndrome, which probably reflects an underlying selective immune defect or a breach in hosts' pulmonary innate or adaptive immune defenses [9, 10, 12]. As in the patients presented here, other investigators have shown the safety and efficacy of prolonged aeAmk therapy for up to 4 years with no late sequelae, including renal dysfunction, vestibular, or ototoxicity [11].

NTM are increasingly recognized as important pulmonary pathogens and increasingly being encountered in susceptible older patients with pre-existing lung disease or Lady Windermere syndrome, although younger patients with no recognizable predisposing features may also present with aggressive pulmonary *M. avium* complex disease [13]. Aerosolized delivery of high drug concentration to lungs is a desirable approach not only for older patients with reduced renal reserves and high risk for systemic toxicity, but also in young adults without comorbidities;

Table 1 Patient, underlying cancer, and nontuberculous mycobacteriosis (NTM) disease characteristics and outcomes in patients with lung infection treated with aerosolized amikacin (aeAmk)

Patient no.	Age (years) and gender	Cancer, disease status	Chemotherapy/ radiation[a]	Co-morbidities (smoking)	ANC/ALC, cells/microliter[b]	Signs and symptoms	Mycobacterial spp., lung involved	Concurrent antimicrobials	Response, duration of aeAMK therapy
1	74, female	Breast, remission	790/4,359	None (−)	8,250/1,710	Chronic cough, dyspnea	*M. kansasii*, RLL, LLL, LUL, lingula	CLR, ETM, RIF	CR, 92 days[c]
2	73, female	Gastric adenocarcinoma, remission	2,240/2,177	Polyserositis (+)	12,700/1,380	Chronic cough, dyspnea	*M. intracellulare*, RLL, LLL, lingula	CIP, CLR	CR, 75 days
3	73, female	None	NA	None (−)	3,600/1,410	Chronic cough, night sweats	*M. avium*, RML, RLL, LLL	ETM, RIF	CR, 201 days[c]
4	69, male	None	NA	COPD (+)	1,840/1,060	None	*M. abscessus*, RML, RLL, LUL, lingula	MOX, CLR	CR, 133 days
5	62, female	None	NA	COPD (−)	4,750/1,590	Chronic cough	*M. kansasii*, RML, RLL	AZT, ETM, RIF	CR, 54 days
6	60, female	Lung squamous carcinoma, advanced	19/229	None (+)	28,420/970	Cough, fever	*M. abscessus*, LUL, LLL	CLR, TMP-SMX	PR, 18 days
7	55, female	Breast, remission	None	None (+)	5,070/1,650	Chronic cough	*M. abscessus*, RUL, RLL, LUL, LLL, lingula	CLR	CR, 59 days
8	53, male	AML, HSCT, partial remission	764/NA	BOOP (−)	9,110/1,520	Cough	*M. intracellulare*, *M. abscessus*, LLL	AZT, CIP, ETM	CR, 38 days
9	51, female	Breast, remission	Active therapy/851	None (+)	4,190/2,280	None	*M. kansasii*, RLL, LUL	CLR, MOX	CR, 277 days[c]

Lung lesions included bilateral pulmonary nodes in all nine patients with varying degree of accompanying bronchiectasis. Cavitary lesion was present in only one patient

[a] Days since the aerosolized amikacin (aeAmk) therapy commenced

[b] Values at the time that aeAMK was given

[c] aeAMK therapy was ongoing at the time of this analysis

NA: not applicable; COPD: chronic obstructive pulmonary disease; AML: acute myelogenous leukemia; HSCT: hematopoietic stem cell transplantation; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; RLL: right lower lobe; RML: right middle lobe; RUL: right upper lobe; LLL: left lower lobe; LUL: left upper lobe; CLR: clarithromycin; ETM: ethambutol; RIF: rifampin; CIP: ciprofloxacin; MOX: moxifloxacin; TMP-SMX: trimethoprim-sulfamethoxazole; AZT: azithromycin; BOOP: bronchiolitis obliterans and organizing pneumonia; CR: complete response was clinical recovery and/or improvement or stable radiographic lung disease; PR: partial response was assigned to patients who had clinical improvement and radiographically non-progressive disease. Patients 6 and 8 died due to advanced cancer and BOOP, 13 and 27 days after NTM diagnosis, respectively

aeAmk may provide much needed ameliorative intervention to preserve lung function and reduce exposure to potentially toxic systemic oral antimicrobials [14].

Aminoglycoside systemic therapy is limited by ototoxicity and nephrotoxicity. In 87 patients with mycobacterial infections, daily versus three times per week aminoglycoside therapy including streptomycin, kanamycin, or amikacin was evaluated [15]. There was no difference in the adverse event profile among the two groups. The risk of ototoxicity was 37% and mostly occurred in older patients in whom a larger cumulative dose had been given [15], whereas vestibular toxicity (9%) and nephrotoxicity (15%) were less common and resolved after the discontinuation of therapy [15]. Aerosolized route of drug delivery is an underappreciated and underutilized modality and has been successfully used for the treatment of serious lung disease due to drug-resistant bacterial or life-threatening invasive fungal pneumoniae [16–18].

The standard anti-*M. avium* complex drug regimens have improved since the introduction of respiratory fluoroquinolones such as levofloxacin or moxifloxacin [19, 20] and new-generation macrolides like azithromycin or clarithromycin [21, 22]. Three drug combinations screened using the radiometric x/y quotient methodology against *M. avium* complex isolates, levofloxacin–ethambutol with a third potential anti-*M. avium* drug (rifampin, roxithromycin, amikacin, or clofazimine), resulted in enhanced activity for 20 drug combinations tested in a previously published report [19]. The current standard anti-*M. avium* complex therapy often includes a macrolide, anti-mycobacterial fluoroquinolone with or without ethambutol; in the era of escalating burden of pNTM disease, which may be less responsive to standard drugs, the feasibility of an alternative non-systemic route of aminoglycoside delivery needs further evaluation [2, 23]. The feasibility and efficacy of aeAmk in combination with limited oral anti-NTM drug(s) for refractory *M. avium* complex lung disease and, importantly, in the primary treatment for pNTM requires validation randomized trials.

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